International Parkinson and Movement Disorder Society

Research Priorities for Gait and Balance Disturbances in Parkinson's Disease

International Parkinson and Movement Disorder Society, Scientific Issues Committee

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Introduction

Gait and balance disturbances are a significant source of disability and morbidity for the majority of patients with Parkinson's disease (PD), and the current understanding of the underlying biology remains insufficient to develop effective therapeutics. The Scientific Issues Committee of the International Parkinson and Movement Disorder Society invited an interdisciplinary panel of experts in the field to consider the knowledge gaps and determine the research strategies with highest potential to generate groundbreaking data.

The invited panel of experts listed at the end of this document held numerous virtual meetings led by MDS-SIC members between 2020 and 2021 centering the discussion on freezing of gait (FOG) as a major problem and balance dysfunction as major contributor to gait disorders in PD. A detailed presentation of this panel discussion is published in Movement Disorders.[1] Here, we present an extract of the panel debate and their consensus about research priorities. From their discussions, it also emerged that there are a number of problems with the data currently generated in clinical studies, which may compromise the application of novel research strategies relying on such data. In response to such concerns raised at the Scientific Panel Discussion, the MDS-SIC asked the expert clinicians in the panel to present their point of view on clinical data problems and potential approaches to address them (for details see[2]). Their proposal is also included in this MDS document, whose objective is to provide recommendations of top research priorities to the scientific community.

Research Priorities

The neuropathologies of FOG and balance dysfunction in PD remain unclear in spite of numerous studies and a vast amount of accumulated data[3-5]. In every aspect of these disorders, there are conflictive, inconclusive or lacking data, which the panel considered in depth. Nevertheless, it stood out that a major barrier to advance the field was a poor understanding of the complex pathophysiology with its diverse anatomical and physiological facets. After reviewing the neural substrates thought to play a mechanistic role[6,7], it was clear that identifying key dysfunctional nodes in the large network involved in posture and locomotion control would be a critical milestone. The motor network spans from the spinal cord to the cortex including several midbrain, cerebellar, basal ganglia and other subcortical circuits, and is also influenced by other networks (non-motor systems), rendering the study of underlying mechanisms of gait disorders highly complex[8-10]. Different components of these networks, which encompass multiple systems, could be affected due to the extension of neurodegenerative or functional changes in PD, thereby adding to the critical compromise of basal ganglia function due to dopamine loss, which is thought to play a major role in gait disorders. The available data also suggest a combination of dysfunctional circuits rather than a single node mechanism disrupting the whole network[7,8,11]. However, this notion as well as further data interpretations into the underlying pathophysiology are still untested hypotheses.

By contrast to the past correlational/observational studies, research driven by hypothesis testing needs to be based on novel functional/operational paradigms to move forward. It is necessary to design experimental models with dynamic operating features to test circuit activity and interactions inside and outside the motor network in different behavioral contexts. These types of models largely rely on technological advances, which now provide a variety of tools to challenge selectively a circuit or cellular population with high resolution and even microscale time precision [12-14]. In addition, a combination of different probes (biochemical, electrophysiological, genetic, imaging) should be applied in studies using experimental models (including refined animal models) for rigorous testing of candidate mechanisms. Also important, inferences derived from these experimental models require further analysis in patients with gait disorders. Therefore, an innovative research strategy also needs to include a clinical phase based on the design of appropriate tests in patients to reveal the mechanisms analogous to human motor behavior.

Such "*multi-scale approach*" has two interdependent components, a preclinical modeling/testing and a clinical analysis. The latter not only provides the basis on which animal/computational models can be constructed or modified (reversed translational approach [15-17]), but also serves to test and validate the discoveries from those experimental models, thereby providing the framework to assess potential causative mechanisms and therapeutic interventions. However, the clinical component needs an innovative approach as well. From analyzing the available data, it could be argued that previous reductionist techniques that have focused on understanding single components of FOG and impaired balance in PD (e.g., imaging, neurophysiology, and epidemiological observations) are precisely the reason for a limited progress. In contrast, a "*systems biology approach*" that applies "big data" analyses from a variety of -*omics* techniques (transcriptomics, metabolomics, proteomics, etc.) in combination with more discrete datasets (imaging, neurophysiology, etc.) to construct models of multiple interacting systems seems a better strategy[18-20]. The integration of a variety of data analyses may also provide better tools for the assessment of modeling outcomes. Such approaches have been increasingly applied in the complex research fields of neuropsychiatric disorders[21]. This discussion led to the panel consensus that a "*multi-scale, systems biology strategy*" needs to be implemented to advance our understanding of the pathogenesis of gait disorders in PD. At the modeling level, "*systems neuroscience strategies*" need to be developed to tackle the role of circuits/networks in the pathophysiology of these disorders.

The panel also considered key aspects of developing successful multi-scale systems biology strategies, which require reliable data sets to inform appropriately the model construction and assess conclusively its outcomes. One of the major challenges to generate reliable data sets is to standardize the definitions, assessments, and measurements of FOG and loss of balance. Indeed, the current characterization, detection, quantification, and several phenomenological issues of these disorders such as their development or progression in PD vary largely across multiple sites and investigators [2]. Settling these issues can provide a framework to generate rigorous data for

use across modeling and clinical studies with diverse approaches. Another critical issue is to form multidisciplinary teams by participating basic scientists/theorists with the skills to apply modern technologies for constructing complex models, and clinicians with critical insights on gait disorders to adequately interpret the outcomes. The constant bidirectional flow of information between disciplines is important for refinement of results back and forth in the translational axis. The ultimate goal of these efforts is to understand better the underlying biology and discover novel strategies for treatment or prevention.

Summary

In summary, a broad consensus of the panel of experts was that *pathophysiology* should be the targeted knowledge gap to set top research priorities in FOG and balance dysfunction in PD. The mechanisms of FOG and loss of postural control in PD seem to involve primarily a basal ganglia dysfunction and other components from a large brain network where motor, sensory, and cognitive/emotional systems intersect. It seems critical to apply multidimensional strategies that could examine interacting networks/systems, which have been seldom used in previous research. The perspective view of the group was that to unravel such mechanisms, it is necessary to develop **systems biology** strategies with a **multi-scale approach** that consists of preclinical modeling and clinical analysis. The clinical portion provides the basis to construct adequate models and allows to test and validate the data generated in those models.

From a modeling standpoint, **systems neuroscience** strategies are primarily needed to study the interacting circuits and networks that control gait and postural balance and may be functionally impacted in PD. These strategies are based on modeling experiments (informed by adequate clinical data) followed by human studies geared to test the model findings. These human studies will require adaptive paradigms to investigate model findings in patients and validate pathophysiologic mechanisms. Both phases rely on applying advanced technologies and analysis of multiple measures to address discrete mechanistic hypotheses. (see[1] for examples of the potential of these research strategies).

Recommendations for Research Priorities

- The application of “Multi-scale, Systems Biology” strategies. This approach will provide multiple analyses of clinical data to inform experimental modeling and back to clinical studies to test the model discoveries.
- The application of “Systems Neuroscience” strategies to develop hypothesis-driven, dynamic studies of circuit function in posture/gait network and extra-network connections, whose dysfunction may become relevant after loss of adequate control by the basal ganglia output in PD.
- The application of such research strategies with the goal to address discrete hypotheses on pathophysiologic mechanisms and model FOG and balance dysfunction in PD.
- The application of research approaches that use testable animal models of PD, particularly refining the existing models, such as the rodents and non-human primates that can reproduce parkinsonian FOG and balance disturbances.
- A broad, multidimensional approach that includes the analyses of biochemical, electrophysiological, genetic, imaging, and other data to address the hypothesis.
- A sequential experimental design that transitions from the modeling phase to the human testing phase based on developing adaptive paradigms for studies in patients.
- The application of the latest advanced technologies that can serve better to test the hypotheses in both modeling and clinical phases.
- Convening a Delphi panel to reach consensual definitions and acceptance levels for measurements and assessments of gait disorders in order to standardize datasets with appropriate training resources.
- Validation studies for novel assessment methodologies and digitized measurement platforms for FOG.
- Multi-modal physiological studies in patients with and without FOG and motor blocks in upper extremities and/or speech.

- Novel modalities of imaging for analysis of multiple systems in behavioral contexts relevant to gait and balance.
- Establishing a prospective meta-analysis for longitudinal studies to address the role of disease progression and medication in the development of FOG and balance disturbances.
- Engaging engineers in the analysis of data from diverse sources and the design of paradigms for human tests of model findings.

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This document has been reviewed and approved by the roster of the Scientific Issues Committee and the leadership of the International Parkinson and Movement Disorder Society.